CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MALEIC HYDRAZIDE

Chemical Code # 000368, Tolerance # 175
SB 950 # 296,
December 1, 1986
Revised 04/21/87, 06/06/89, 10/19/90, and 11/29/95

I. DATA GAP STATUS

Combined, rat (Chronic & Onco):	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome effects: No data gap, possible adverse effect

DNA damage: No data gap, possible adverse effect

Neurotoxicity: Not required at this time

Toxicology one-liners are attached.

All record numbers through 119305 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T951129
Revised by H. Green & M. Silva.

NOTE: Maleic hydrazide (DPN 175) is the DPR-recommended "Lead Chemical" for the diethanolamine (DPN 50771) and potassium (DPN 50772) salts of maleic hydrazide. Registration of the diethanolamine salt has been withdrawn in California.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED TOXICITY, RAT

** 50772-003 119035, "Maleic Hydrazide/104 Week Dietary Combined Chronic Toxicity/Oncogenicity Study in Rats with 52 Week Interim Kill", (C.J Perry, A. Strutt, J.P. Finn and P. Hudson, Uniroyal Chemical Co., Inc., Laboratory Project ID: IRI 437944, 11/28/91). Maleic Hydrazide (72.5%-73.8% pure; Potassium Salt) was fed in diet to Sprague-Dawley rats at 0, 25, 500 or 1000 mg/kg per day for 52 (20 rats/sex/dose) and 104 (50/sex/dose) weeks. The mean achieved doses were: 25, 503 & 1008 mg/kg (males) and 25, 503 & 1003 mg/kg (females). Systemic NOEL = 25 mg/kg (based on reduced body weight). Oncogenic NOEL > 1000 mg/kg (No treatment-related oncogenicity was observed at any dose.) ACCEPTABLE. (Kishiyama & Silva, 11/20/95).

175-006, 017; 016988; "Toxicological Studies of Chemical Additives. 3. Maleic Hydrazide (1,2-dihydropyridazine)-3,6-dione." (Food Research Lab. Inc., 6/10/55, Laboratory No. 62006). Maleic hydrazide (diethanolamine formulation and sodium salt (83.3%), 30% maleic hydrazide in liquid form); sodium maleic hydrazide was tested at 0, 0.5, 1.0, 2.0 and 5.0% in the diet corrected for purity and with diethanolamine maleic hydrazide at 1.0% and 0.1% for 104 weeks in rats (strain not specified); approx 20/group; early report, does not meet guidelines; summary data except for pathology study with partial list of individual animals; incomplete with pages missing. **No adverse effect** indicated. **Unacceptable** (multiple major deviations from the guidelines). In addition, the animals were mated after 12 weeks on the test diets with additional matings over the lifetime of the animals. The offspring of the second litter were used to produce the F_2 litters and study was continued to produce two F_3 litters. (Gee, 7/31/85)

175-016; 000730; "Chronic Toxicity for Rats"; This document contains a summary of a chronic toxicity study in rats. No data were presented. No worksheet was done (Morris, 06/05/89).

CHRONIC TOXICITY, DOG

** 50772-002 112907, "Maleic Hydrazide/52 Week Dietary Toxicity Study in Dogs", (B.T. Anderson and P. McDonald, Inveresk Research International, Tranent, Scotland, Report # 641540, 26 July 1991). Maleic hydrazide, potassium salt (75% pure at study termination) was fed in diet for 52 weeks at 0 (Special Diets Services Dog Diet A), 750, 2500, or 25000 ppm to Beagle dogs (6/sex/dose). Chronic NOEL = 750 ppm (Body weights were decreased in both sexes at 25000 ppm. Body weight gains were decreased in both sexes at $\geq$ 2500 ppm. One high dose male was sacrificed in extremis during week 28. AP and ALT were increased at 25000 ppm. Heart weights were decreased and thyroid weights were increased, primarily at 25000 ppm. Histopathology was observed in liver and thyroid for both sexes at 25000 ppm: Prominent lobulation and perivascular inflammation in the liver and foci of epithelial hypertrophy of the thyroid.) **No adverse effects.** (Green & Silva, 11/17/95).

175-006 16988 This volume contains the introductory paragraph of a dog study. The next page, numbered 41, contains the reference list. M. Silva, 11/20/95.

ONCOGENICITY, RAT

175-016; 000733; "Maleic hydrazide, carcinogenicity study in rats." (Publication in Toxicology, 19 (1981) 139-150, Natl. Inst. Pub. Health, Holland (1980), van der Heijden et al.) Maleic hydrazide (Technical grade, 10.1% water w/w with anhydrous purity of 99% and hydrazine impurity at < 1.5 mg/kg maleic hydrazide); tested at 0, 1.0 and 2.0% corrected for purity in the diet for 28 months with Wistar rats; 55 rats/sex/dose group for controls and 1% and 65 rats/sex at 2%; decrease in body weight early in study and increase in protein and protein/creatinine at 6 and 12 months at 1.0 and 2.0%; increase in water intake at 2%; no tumorigenic effect. Possible **adverse effect** indicated: chronic toxicity in kidney function; NOEL < 1% (kidney function, decreased weight gain early in study); **unacceptable** and not upgradeable (incomplete necropsy/histopathology data, no individual animal data). (Gee, 7/31/85)
EPA 1-liner: Core Minimum Data. Negative for oncogenicity at feeding levels of 1 percent and 2 percent. [From memo contained in Record 050919.]

175-027; 066110: This document contains the full EPA evaluation of the rat oncogenicity study (CDFA doc. # 175-016, rec. # 000733). The major deviation from FIFRA guidelines in this study was that only 10 rats / sex in the control and high dose groups were subjected to full histopathological examination at the end of the study. The study is unacceptable and not upgradeable.

175-017; 016989: This document contains a summary of CDFA doc. # 175-016, rec. # 000733 and summaries of other chronic and reproductive studies. No worksheet was done (Gee, 07/31/85; Morris, 06/05/89).

ONCOGENICITY, MOUSE

** 175-020, 021; 036563, 036564 (originally reviewed as 007 & 008, 16991 & 924557); "Lifetime oncogenicity study in mice." (IRDC, 10/8/81, 399-007 Maleic hydrazide (potassium salt, 90%,

technical) tested at 0, 1000, 3200 and 10,000 ppm in the diet in a 23 months study with Charles River CD-1 mice; 50/sex/dose group; average compound consumptions for males were 157, 509 and 1545 mg/kg/day and for females were 189, 598 and 1811 mg/kg/day; increase in mortality .25% at 98 weeks and the study was terminated; **no adverse effect**; initially reviewed as unacceptable but upgradeable with submission of characterization of test article, diet analysis and stability data. These are contained in Record 050919, Document 175-025, upgrading the study to **acceptable** with no adverse oncogenic effect. (Gee, 8/1/85 and 4/20/87).

EPA 1-liner: Core Supplementary. Negative for oncogenicity at oral doses of 100, 3200 and 10,000 ppm. [From EPA memo contained in Record 50919.]

175-025; 050919: Supplement to 036563. Information on test article, diet analyses, justification of dose selection and copy of memo from EPA on status of study.

175-016; 000731; "Carcinogenicity study of the pesticide maleic hydrazide in mice." (Publication in: Toxicology, 24 (1982) 169-173, Cabral, J. R. P. and V. Ponomarkov, IARC, Lyon, France, 1982) Maleic hydrazide (98.5% free acid with 0.6 ppm hydrazine) with and without vehicle (olive oil, tricaprylin) tested by four weekly subcutaneous injections at 5, 10, 20 and 20 mg/rat on days 1, 7, 14 and 21 after birth or by oral gavage with a weekly dose of 510 mg/kg body weight for 120 weeks in C57BL/B6 mice; 51 males and 49 females without vehicle and 13 males and 13 females with vehicle control; 40 males and 42 females at 510 mg/kg/week; subcutaneous injection induced high mortality (conc. not given). **No adverse effect** indicated. **unacceptable** (protocol, missing information). (Gee, 7/31/85)
EPA 1-liner: Core Supplementary data. Negative for tumor induction at oral doses of 510 mg/kg/week. [From memo from EPA contained in Record 50919.]

Summary Statement: EPA has pooled the data of these two studies to determine that, collectively, they provide adequate evidence to conclude that maleic hydrazide is not oncogenic for mice. CDFA initially rejected both studies but now thinks that with the submission of the requested information on the test article and justification of dose selection, the study by IRDC can be upgraded to acceptable with minor variations from guidelines, thus fulfilling the category for oncogenicity study in the mouse. (Gee, 4/20/87)

REPRODUCTION, RAT

** 175-022; 036566; "Two-Generation Reproduction Study with KMH in Rats, study #81065". (Hazleton Raltech, Inc., 5/11/83) Potassium maleic hydrazide, technical, lots 034100001X Skid 2 and 03487001X, white crystalline powder, 99%; fifteen male and 30 female rats per group were fed 0, 1000, 10,000, 30,000 or 50,000 ppm; no adverse effect in reproduction reported; decrease weight gain in pups at 50,000 ppm and 30,000 ppm; NOEL = 10,000 ppm, **no adverse effect**; complete; **acceptable**. (Gee, 12/17/85)

175-017; 016982: Summary of 036566.

175-016; 000732: This document contains a summary of CDFA doc. # 175-022, rec. # 036566. No worksheet was done (Morris, 06/05/89).

175-003; 924559; (Food Research Laboratory, Inc., 7/16/53) Maleic hydrazide (sodium salt; purity unknown) tested at 0, 0.5, 1.0, 2.0 and 5.0% in the diet in a 2-generation, 2 litters/generation study in rats (strain unspecified); 9-10 male and 10 female rats/dose group. **No adverse effect** indicated. **Unacceptable** (purity of compound, diet analysis, not enough animals, no histopathology study) (Gee, 7/30/85)

TERATOLOGY, RAT

175-006; 924558; "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in rats." (Publication in: J. Environ. Sci. Health B14: 563-577 (1979), Bureau of Chem. Safety, Canada, 1979) Maleic hydrazide (97%) tested at 0, 400, 800, 1200 and 1600 mg/kg by oral gavage on days 6-15 of gestation in Wistar rats; 18-20 females/dose group; sacrificed on day 22; summary data only; **unacceptable**. **No adverse effect** report. (Gee, 7/30/85)

028 075196, "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats, Version with Raw Data Sheets Appended", (Khera, K.S., Whalen, C., Trivett, G. and Angers, G., Bureau of Chemical Safety, New Research Centre, Turney's Pasture, Ottawa, Canada, 1979, published in the J. Environ. Sci. Health, B14(6), 563-577, 1979). Maleic hydrazide (97% pure) was administered by gavage days 6-15 of gestation (positive vaginal smear = day 1 of gestation) at 0 (corn oil), 400, 800, 1200, and 1600 mg/kg/day (limit test at 1000 mg/kg/day) to 20 mated Wistar female rats/group. **No adverse effect** indicated. Maternal NOEL = 1600 mg/kg/day. Developmental NOEL = 1600 mg/kg/day (No fetal or maternal toxicity was observed at any dose.) **Not acceptable** (no analysis of dosing material, fewer than 20 pregnant females/group, no clinical signs). Possibly upgradeable with submission of requested information. This is a more complete version of volume/record#: 006 924558. (H. Green & M. Silva, 10/4/90).

175-017; 016980: The same as doc. # 175-006, rec. # 924558. No worksheet was done (Morris, 06/02/89).

246-005; 023505: The same as doc. # 175-006, rec. # 924558. No worksheet was done (Morris, 06/02/89).

175-025; 050912; "Assessment of Teratological Effect and Developmental Effect of Maleic Hydrazide Salts in Rats." Journal article Bull Environ. Contam. Toxicol. (1984) 33:184-192 (1984, Institute of Toxicology/National Food Institute, Denmark). Monoethaneolamine maleic hydrazide, aqueous solution at 360 g/l, and the sodium salt of maleic hydrazide, 97% w/w Na-MH, 73% w/w maleic hydrazide, hydrazine 46 ppm; given by gavage days 6-15 at 0, 500, 1500 and 3000 mg/kg gestation days 6-15 and at 3000 mg/kg (in the diet) days 1-21 to Mol: WIST rats, 24/group the first experiment and 44/group (53 control) the second experiment; additionally, 12/group were given 3000 mg/kg day by gavage gestation days 6-9, 9-12, 12-15; rats in the 1st experiment at 3000 mg/kg showed decreased body weight and weight gain. **No teratological effect** indicated. Maternal toxicity NOEL = 1500 mg/kg/day; developmental NOEL > 3000 mg/kg.

Incomplete. **Unacceptable**, upgradeable (No individual data, missing data. A full report of this study is requested). (Parker, 4/2/87).

** 175-030 086426, "Maleic Hydrazide/Teratogenicity Study in Rats", (J. A. Wilson and K. P. Hazelden, Inveresk Research International, Elphinstone Research Centre, Musselburgh, Scotland, 4/4/90). Potassium Maleic Hydrazide Technical (72.5 % (w/w) purity, batch #: AC1035-04A) was administered by gavage on gestation days 6 through 16 (detection of sperm or a copulatory plug = day 0) at mean analytical concentrations of 0 (distilled water), 30, 300, and 1000 mg/kg/day (limit test) to 23 - 25 mated Sprague-Dawley Charles River CD (outbred albino) female rats per group. **No maternal or fetal effects** were observed, however the study is **acceptable** by the limit test. Maternal NOEL $\geq$ 1000 mg/kg/day. Developmental $\geq$ 1000 mg/kg/day. (H. Green & M. Silva, 10/4/90).

TERATOLOGY, RABBIT

** 175-022; 036565; "Teratology Study in Rabbits with Potassium Salt of Maleic Hydrazide." (IRDC, 399-051, 5/6/83) Potassium maleic hydrazide, technical, lot 03571001X, white powder sixteen per group given 0, 100, 300 or 1000 mg/kg by oral gavage on days 7-27 of gestation; dosing based on a preliminary study; development NOEL > 1000 mg/kg, maternal NOEL = 300 mg/kg; **no adverse effect** complete; **acceptable**. (Gee, 12/26/85)

175-017; 016981: Summary of 36565.

GENE MUTATION

Iv ϖιϖο systems

175-023, 025; 036568; "Sex Linked Recessive Lethal Assay in Drosophila: Evaluation of Maleic Hydrazide (potassium salt) Technical in Distilled Water 26.78% (w/v)." (Litton Bionetics,

Inc., 2/78) Males were exposed as larvae and adults to 0.4 and 1% a.i.; emergence delay was noted at both concentrations; males were mated once to 3-5 females; F_1 mated and F_2 scored; no repeat experiment, mated only once to get F_1; **no adverse effect** indicated; **unacceptable** (no repeat trial, inadequate number of chromosomes tested). (Gee, 12/12/85; B Davis, 4/87)

175-006; 924561: This is an incomplete version of doc. #'s 175-023, 025; rec. # 036568.

175-017; 016987: This is an incomplete version of doc. #'s 175-023, 025; rec. # 036568.

Bacterial systems

175-024; 050055; "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems." (Publication in: Mutation Res., 116; 185-216 (1983), Moriya, M. et al, Inst. of Eviron. Tox. Japan 5/18/82). Maleic hydrazide was tested in the Ames test with 5 strains (TA100, TA98, TA1535, TA1537 and TA1538) with and without S9 activation; **no adverse effect** indicated. **Unacceptable** (summary only-incomplete information for independent health assessment). (Choy, 12/1/86)

175-025; 050914: This document contains an exact duplicate of CDFA doc. # 175-024, rec. # 050055 (Morris, 06/06/89).

175-024; 050056; "Detection of Carcinogens as Mutagens in the Salmonella/Microsome test: Assay of 300 Chemicals." (Publication in: Proc. Nat. Acad. Sci., USA, 72: 5135 - 5139, 1975, U.C. Berkeley, 10/10/75.) Maleic hydrazide was tested in the Ames test with 4 strains (TA100, TA98, TA1535, TA1537) with and without S9 activation; **no adverse effect** indicated. **Unacceptable** (summary only - incomplete information for independent health assessment). (Choy, 12/1/86)

175-025; 050915: This document contains an exact duplicate of CDFA doc. # 175-024, rec. # 050056 (Morris, 06/06/89).

Mammalian system

175-006; 924560; "Mutagenicity Evaluation of KMH Solution in the Mouse Lymphoma Forward Mutation Assay: Final Report." (Litton Bionetics, 5/81, LBI Project No. 20989) Maleic hydrazide (27.6% in water, 1.79 M, pH 9.00) tested at 0, 0.5, 0.625, 1.250, 2.5, 5.0, and 10.0 ul/ml in the $TK^{+/-}$ to $TK^{-/-}$ forward gene mutation test in L5178Y mouse lymphoma cells; 3 replicates / treatment implied but data were presented as total colonies in a treatment group; 2-day expression time; with and without S9 activation. **no adverse effect** indicated. **Unacceptable**, not upgradeable (justification of highest dose level, no indication of selective agents for mutant selection, problem with plates lost due to contamination in first trial; second trial terminated due to lack of cytotoxicity). (Gee, 07/31/85)

175-025; 050913: This document contains the raw data for CDFA doc. # 175-006, rec. # 924560. No worksheet was done (Gee, 04/20/87).

175-017; 016985: This document contains a summary of the CDFA doc. # 175-006, rec. # 924560. No worksheet was done (Morris, 06/05/89).

175-017; 016983: "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse", Toxicology and Applied Pharmacology, 23:288-325 (1972). This document contained the abstract of a paper in the open literature. No data were presented. No worksheet was done (Gee, 07/31; Morris, 06/05/89).

** 175-028 075194, "Reverse Mutation in Σαλμονελλα τψπηιμυριυμ", (Forster, R. and Meli, C., Life Science Research, Roma Toxicology Centre S.P.A., Italy, report # 131004-M02988, 7/21/89). Maleic hydrazide (potassium salt, 88.69% pure, lot #: MDD 021288) was used in a reversion assay with Σαλμονελλα τψπηιμυριυμ strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 (2 trials in triplicate) with and without S9 (S9 from liver fractions of phenobarbital and beta-naphthoflavone induced young male Sprague-Dawley rats) at 0, 625, 1250, 2500, 5000, and 10000 ug/plate (limit test). **No increase in reversion frequency was observed**. **Acceptable**. (H. Green & M. Silva, 10/12/90)

CHROMOSOME EFFECTS

175-006; 924563; "Mutagenicity Evaluation of KMH Solution in the Mouse Micronucleus Test: Final Report." (Litton Bionetics, 8/81, LBI Project No. 22109) Maleic hydrazide (potassium salt, 27.6% in distilled water) tested at 0, 0.02 , 0.17, 1.3 and 7.5 gm/kg by oral gavage for micronucleus test in Charles River CD-1 mice; 12 mice/sex/dose group; LD_{50} .7 mg/kg and 11/24 mice treated with 7.5 gm/kg died within 24 hours; 3 mice/sex/dose group were sacrificed at 24, 48 and 72 hours; **possible adverse effect**; **unacceptable,** not upgradeable (errors in dosing; data on positive controls from two trials did not agree). (Gee, 7/31/85)

175-025; 050913: This document contains the raw data for CDFA doc. # 175-006, rec. # 924563. No worksheet was done (Gee, 04/20/87).

175-025; 050916: This document contains the protocol for CDFA doc. # 175-006, rec. # 924563. No worksheet was done (Gee, 04/20/87).

175-006; 924562; "Mutagenicity Evaluation of Maleic Hydrazide in the Mouse Bone Marrow Cytogenetic Analysis; Final Report." (Litton Bionetics, 3/78, LBI Project No. 20840) Maleic hydrazide (potassium salt, purity unspecified) tested at 0, 0.5, 1.0 and 5.0 gm/kg in Charles River CD-1 mice (route of exposure ?); 24 males/dose group; no females tested; colcemid injected 2 hours before sacrifice at 6, 24 and 48 hour after treatments; 50 cells/slide scored for each animal; **no adverse effect** indicated - insufficient information for health assessment; **unacceptable**, not upgradeable (only males tested, missing data) (Gee, 7/30/85)

175-023; 036571: Duplicate of 924562 plus copies of the pages of raw data not previously submitted.

175-017; 016986: This document contains a summary of the doc. # 175-006, rec. # 924562. No worksheet was done (Morris, 06/05/89).

175-025; 050917: This document contains an exact duplicate of CDFA doc. # 175-006, rec. # 924562 (Morris, 06/06/89).

SUMMARY Although each of the studies was evaluated as unacceptable, collectively there are sufficient data to determine there is evidence of chromosomal damage with maleic hydrazide. Thus, the data requirement for this test area is fulfilled (Gee, 04/21/87).

DNA DAMAGE

175-006; 924564; "Final Report on the Genetics Activity of KMH-solution in the Bacterial DNA Repair Test." (Litton Bionetics, 5/81, LBI Project No. 20988) Maleic hydrazide (potassium salt, 27.6%) tested at 0, 0.01, 0.1, 5.0, 10.0, 25.0 and 25.0 and 50.0 ul/plate in E. coli DNA repair test using strains W3110^{+} and p3478^{-}; measure of zone of inhibition; **no adverse effect** indicated. **Unacceptable**, not upgradeable (description of protocol needs to be more specific, no evidence of cytotoxicity - no test.) (Gee, 7/31/85)

175-025; 050913: This document contains the raw data for CDFA doc. # 175-006, rec. # 924564. No worksheet was done (Gee, 04/20/87).

175-017; 016984: This document contains a summary of doc. # 175-006, rec. # 924564

**** 175-028 075195**, "Maleic Hydrazide, Potassium Salt (KMH) In the Rec - Assay with Bacillus subtilis (Preincubation Method)", (Hoorn, A.J.W., Hazleton Biotechnologies, The Netherlands, Study # E-9836-0-404-P, 7/29/88). Maleic hydrazide potassium salt (KMH) (97% pure, lot #: MDD 021288) was used in a recombination assay with Bacillus subtilis strains H17 (rec+) and M45 (rec-) with and without S9 (S9 was obtained from Aroclor 1254 induced adult male Sprague-Dawley rat livers) at 0, 1, 10, 100, 500, 1000, 2500, 5000, and 10000 µg/plate. Data from three trials (all with and without S9) were reported. **Adverse effect**: DNA damage was observed when S9 was used. **Acceptable**. (H. Green & M. Silva, 10/12/90)

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL STUDIES

175-017; 016990; "Chronic Studies in Mice of the Effect of Skin Painting with Tobacco Smoke Condensates", laboratory no. 85676; Food and Drug Research Laboratories; 01/12/66; This document contains a summary of a one-year, skin-painting study in mice. No significant difference were reported for exposure to cigarette condensates from untreated versus maleic hydrazide-treated tobacco. No worksheet was done (Morris, 06/05/89).